The present invention is directed, in part, to methods of optimizing the therapeutic efficacy of 6-mercaptopurine drug treatment of an immune-mediated gastrointestinal disorder. A method of the invention for optimizing therapeutic efficacy includes the steps of administering a 6-mercaptopurine drug to a subject and determining the level of 6-thioguanine in the subject. A level less than 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount of 6-mercaptopurine drug subsequently administered to the subject. A level of 6-thioguanine greater than a level corresponding to about 400 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of 6-mercaptopurine drug subsequently administered to the subject. The invention also provides methods of reducing toxicity associated with 6-mercaptopurine drug treatment of an immune-mediated gastrointestinal disorder. A method of the invention for reducing toxicity associated with 6-mercaptopurine drug treatment includes the steps of administering a 6-mercaptopurine drug to a subject having an immune-mediated gastrointestinal disorder and determining a level of a 6-mercaptopurine metabolite in the subject, where a level greater than a predetermined toxic level of the 6-mercaptopurine metabolite indicates a need to decrease the amount of 6-mercaptopurine drug subsequently administered to the subject. Thus, the present invention can be used to optimize the therapeutic efficacy of 6-mercaptopurine drugs while minimizing toxic side effects.

Regarding the New Claims

New claims 35 to 46 have been added. Support for new claims 35 to 46 can be found in claims 7 and 19, as filed, and, for example, on page 8, line 12, to page 9, line 3; page 16, lines 1-31; and page 24, line 3, to page 26, line 9, which indicates that a method of optimizing therapeutic efficacy and reducing toxicity associated with 6-mercaptopurine drug treatment of an immune-mediated gastrointestinal disorder can include the steps of administering a 6-mercaptopurine drug to a subject having an immune-mediated gastrointestinal disorder; and determining a level of a 6-mercaptopurine metabolite in the subject having the immune-mediated gastrointestinal disorder, wherein a level of the 6-mercaptopurine metabolite less than a predetermined minimal therapeutic level indicates a need to increase the amount of 6-mercaptopurine drug subsequently administered to the subject, thereby increasing therapeutic efficacy, and wherein a level of the 6-mercaptopurine metabolite greater than a predetermined toxic level of the 6-mercaptopurine metabolite indicates a need to decrease the amount of 6-mercaptopurine drug subsequently administered to the subject, thereby reducing toxicity associated with 6-mercaptopurine drug treatment of the immune-mediated gastrointestinal disorder. Therefore, the new claims are supported by the specification and do not add new matter. Accordingly, Applicants respectfully request entry of the new claims.

Rejection under 35 U.S.C. § 112, second paragraph

The rejection of claims 1 to 34 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention, is respectfully traversed. The Office Action states that in claims 1, 7, 13, 19, 29 and 30, the term "drug" within the term "6-mercaptopurine drug treatment" is superfluous and can be deleted without changing the meaning of the term or claims. The Office Action also states that in claim 1, step (a), the "a" before "6-mercaptopurine drug" is superfluous.

Applicants respectfully submit that claims 1 to 34 are clear and definite as written. The specification discloses, for example, that the term "6-mercaptopurine drug" refers to any drug that can be metabolized to an active 6-mercaptopurine metabolite that has therapeutic efficacy (page 9, lines 4-15). The specification further discloses exemplary 6-mercaptopurine drugs such as 6-mercaptopurine and azathioprine (page 9, lines 7-9) and additional 6-mercaptopurine drugs such as 6-methylmercaptopurine riboside and 6-thioguanine (page 9, lines 16-23). Figure 1 illustrates that azathioprine (AZA), for example, is metabolized to a 6-mercaptopurine metabolite. Thus, in view of the teachings set forth in the specification, "6-mercaptopurine drug" means 6-mercaptopurine itself or another drug such as azathioprine that can be metabolized into an active 6-mercaptopurine metabolite. Accordingly, Applicants submit that the term "6-mercaptopurine drug" is clear and definite and respectfully request the Examiner

remove this ground for rejecting the claims under 35 U.S.C. § 112, second paragraph.

The Office Action also states that claims 4, 10 and 22 are indefinite because the term "autoimmune enteropathy" is synonymous with "IBD," or included within the scope of "IBD" or "Crohn's disease." In addition, the Office Action states that the relationship of the five remaining recited disease conditions to IBD or Crohn's disease is unclear.

Applicants respectfully submit that the claims are clear and definite as written. The specification teaches that the term "immune-mediated gastrointestinal disorder" means a non-infectious disease of the gastrointestinal tract or bowel that is mediated by the immune system or cells of the immune system (page 10, line 30, to page 11, line 2). As set forth in the specification, such an immune-mediated gastrointestinal disorder can be, for example, an inflammatory bowel disease such as Crohn's disease or ulcerative colitis (page 11, line 2, to page 14, line 9). In addition, an immune-mediated gastrointestinal disorder can be lymphocytic colitis, microscopic colitis, collagenous colitis, autoimmune enteropathy, allergic gastrointestinal disease or eosinophilic gastrointestinal disease (page 11, lines 2-8, and page 14, lines 10-17). In this regard, the specification teaches characteristics of each of the recited diseases: lymphocytic colitis, microscopic colitis, and collagenous colitis (page 14, line 24, through page 15, line 4); autoimmune enteropathy (page 15, lines 5-16); allergic

gastrointestinal disease (page 15, lines 22-30); and eosinophilic gastrointestinal disease (page 15, lines 17-22).

In regard to autoimmune enteropathy, the specification teaches that this disease is a syndrome of severe secretory diarrhea and marked enterocolitis in association with diagnostic circulating antibodies to enterocytes (page 15, lines 5-16). Autoimmune enteropathy is most often seen in infancy and can be associated with other autoimmune diseases. Inflammatory bowel disease (IBD) means Crohn's disease and ulcerative colitis (page 11, lines 9-24). Crohn's disease is a disease of chronic inflammation that can involve any part of the gastrointestinal tract, commonly the distal portion of the small intestine and cecum (page 11, lines 16-24). Ulcerative colitis (UC) is a disease of the large intestine characterized by chronic diarrhea, with cramping abdominal pain, rectal bleeding, and loose discharges of blood, pus and mucous (page 12, line 29, to page 13, line 9). Thus, as disclosed in the specification, autoimmune enteropathy is a clinically and diagnostically distinct disease from inflammatory bowel diseases (IBDs) such as CD and UC.

Furthermore, lymphocytic colitis, microscopic colitis, collagenous colitis, allergic gastrointestinal disease and eosinophilic gastrointestinal disease are also clinically and diagnostically distinct diseases from IBDs such as CD and UC. For example, lymphocytic colitis and microscopic colitis is a clincopathological syndrome characterized primarily by lymphocytic infiltration of the epithelium (page 14, lines 24-27). Collagenous colitis is a disease defined by the presence

of a collagenous band below the surface epithelium, accompanied by an increase in inflammatory cell infiltrate (page 14, lines 27-31). Allergic gastrointestinal disease is a food allergy disease (page 15, lines 22-30). Eosinophilic gastrointestinal disease is characterized by a dense infiltration of eosinophils in one or more areas of the gastrointestinal tract, variable intestinal symptoms and usually a peripheral eosinophilia (page 15, lines 17-22). Thus, as disclosed in the specification and described above, each of these diseases is clinically and diagnostically distinct from IBDs such as CD and UC.

In summary, Applicants respectfully submit that the immune-mediated gastrointestinal disorders recited in claim 4, lymphocytic colitis, microscopic colitis, collagenous colitis, autoimmune enteropathy, allergic gastrointestinal disease and eosinophilic gastrointestinal disease, are clinically and diagnostically distinct diseases from inflammatory bowel diseases such as CD and UC. Therefore, Applicants respectfully submit that claim 4 is clear and definite and, accordingly, request that this ground for rejecting the claim under 35 U.S.C. § 112, second paragraph, be removed.

Rejection under 35 U.S.C. § 103(a)

The rejection of claims 1 to 34 under 35 U.S.C. § 103 (a) as allegedly obvious over Sandborn, Scand. J. Gastroenterol. Suppl. 225:92-99 (1998), (hereinafter "the Sandborn reference") in view of Sandborn, U.S. Patent No. 5,733,915, (hereinafter "the Sandborn patent") and further in

view of Berkow et al., The Merck Manual of Diagnosis and Therapy 16th Ed., Merck & Co., Rahway, NJ, pp. 328-330, pp. 826-828 and pp. 830-845 (1992), (hereinafter "Berkow") is respectfully traversed. The Office Action states that the Sandborn reference is a review article describing the medicinal activity of azathioprine (AZA) and 6-mercaptopurine (6-MP) for treatment of Crohn's disease, inflammatory bowel disease, ulcerative colitis and related conditions. The Office Action also indicates that the Sandborn reference reports toxic effects of AZA and 6-MP administration, including pancreatitis, allergic reactions, drug hepatitis, and leukopenia. In regard to the Sandborn patent, the Office Action states that this reference describes the treatment of Crohn's disease by administration of azathioprine and 6-mercaptopurine and further specifies ranges for blood cell concentrations of 6-thioguanine and 6-methylmercaptopurine. The Berkow reference is cited as allegedly reporting that azathioprine and 6-mercaptopurine are effective in the treatment of Crohn's disease but that side effects such as pancreatitis and leukopenia are indicia of excessive immunosuppressive drug concentrations and must be avoided.

Applicants respectfully submit that the claimed methods are unobvious over the cited references. The Sandborn reference is a review article describing the pharmacology, patient response, various formulations and routes of administration of 6-mercaptopurine and azathioprine for treatment of Crohn's disease and ulcerative colitis. However, the Sandborn reference, alone or in combination with the Sandborn patent or Berkow, does not teach or suggest the claimed methods of optimizing

therapeutic efficacy and/or reducing toxicity associated with 6-MP drug treatment of an immune-mediated gastrointestinal disorder.

Regarding claims 1 to 6

In regard to claim 1 and dependent claims 2 to 6, Applicants submit that the Sandborn reference does not teach or suggest a method for optimizing therapeutic efficacy of 6-MP drug treatment of an immune-mediated gastrointestinal disorder by administering a 6-MP drug to a subject having an immune-mediated gastrointestinal disorder and determining a level of 6-thioguanine (6-TG) in the subject, where a level of 6-TG less than about 230 pmol per $8x10^8$ red blood cells (RBCs) indicates a need to increase the amount of 6-MP drug subsequently administered to the subject and where a level of 6-TG greater than about 400 pmol per $8x10^8$ RBCs indicates a need to decrease the amount of 6-MP drug subsequently administered to the subject. Absent such a teaching or suggestion, the Sandborn reference cannot render the claimed methods obvious.

In regard to the Sandborn patent, this reference appears to describe the levels of 6-thioguanine nucleotide and 6-methylmercaptopurine in Crohn's disease patients who received AZA intravenously for 36 hours followed by oral administration of AZA at 50 to 100 mg/day or 100 to 150 mg/day if no clinical response was observed by 4 to 8 weeks (column 5, lines 7-23). The Sandborn patent does not teach or suggest the claimed methods of optimizing therapeutic efficacy associated with 6-MP drug

treatment by determining a level of 6-thioguanine, where a level less than about 230 pmol per $8x10^8$ RBCs indicates a need to increase the amount of 6-MP drug subsequently administered and wherein a level greater than about 400 pmol per $8x10^8$ RBCs indicates a need to decrease the amount of 6-MP drug subsequently administered. At best, the Sandborn patent merely describes the levels of 6-thioguanine nucleotide and 6-methylmercaptopurine associated with a specific AZA treatment regimen.

Moreover, the Sandborn patent actually teaches away from the claimed invention. The Sandborn patent reports that "[C]linical response did not correlate with 6-TGN or 6-MeMP concentrations at the AZA dose studied" (column 7, lines 51-52). The Sandborn patent further indicates that there was no significant correlation between the Crohn's disease activity index (CDAI) and the RBC 6-TGN or 6-MeMP concentrations at week 4, week 8 or week 16 (column 7, lines 61-67). Therefore, one skilled in the art would have had no motivation to combine the description in the Sandborn patent related to measuring the level of 6-thioguanine nucleotide or 6-methylmercaptopurine with the general description in the Sandborn reference related to toxic effects of AZA/6-MP treatment of inflammatory bowel disease to obtain the claimed methods of optimizing therapeutic efficacy of 6-MP drug treatment by determining a level of 6-TG and either increasing or decreasing the amount of 6-MP drug subsequently administered if the 6-TG level is less than about 230 pmol/$8x10^8$ RBCs or greater than about 400 pmol/$8x10^8$ RBCs, respectively.

In regard to the specific levels of 6-MP metabolites described in the Sandborn patent, Applicants respectfully submit that the levels described in the Sandborn patent are significantly higher than the claimed levels of 6-MP metabolites. For example, the Sandborn patent states that 6-thioguanine nucleotide concentrations are preferably about 50 to 400 pmol/10^8 RBCs after intravenous therapy or about 50 to 500 pmol/10^8 RBCs after intravenous therapy while the patient is taking AZA orally (column 2, lines 49-54). In contrast, the predetermined minimal therapeutic level of 6-TG recited in claim 1 is about 230 **pmol/8x10^8** RBCs. Upon conversion to the same factor, the levels described in the Sandborn patent of 50 to 400 **pmol/10^8** RBCs equals 400 to 3200 **pmol/8x10^8**; the levels of 50 to 500 **pmol/10^8** RBCs equals 400 to 4000 **pmol/8x10^8**. These levels are significantly higher than the predetermined minimal therapeutic 6-TG level of about 230 pmol/8x10^8 RBCs recited in claim 1. In regard to a predetermined toxic level of 6-TG, the recited level is about 400 pmol/8x10^8 RBCs. Thus, the claimed predetermined toxic level of 6-TG is actually the <u>minimal</u> level of 6-thioguanine nucleotide described in the Sandborn patent.

In regard to Berkow, the Office Action states that Berkow reports that azathioprine and 6-mercaptopurine are effective in the treatment of Crohn's disease but that side effects such as pancreatitis and leukopenia indicate excessive drug concentrations, which should be avoided (pages 833-834). Berkow appears to be a text book directed to diagnosis and therapy of various diseases and describes the use of azathioprine and 6-mercaptopurine as effective treatments of Crohn's disease.

Berkow indicates that side effects of allergy, pancreatitis or leukopenia "must be carefully watched for." Therefore, Berkow merely states that treatment with azathioprine or 6-mercaptopurine may have side effects that should be monitored. Moreover, the reference fails to describe any relationship between 6-TG or 6-MMP levels and side effects. As such, Berkow fails to teach or suggest the claimed methods of optimizing therapeutic efficacy of 6-MP drug treatment by determining a level of 6-TG, where a level less than about 230 pmol/$8x10^8$ RBCs indicates a need to increase the amount of 6-MP drug subsequently administered and where a level greater than about 400 pmol/$8x10^8$ RBCs indicates a need to decrease the amount of 6-MP drug subsequently administered. Absent such a teaching or suggestion, Berkow cannot render the claimed methods obvious.

Therefore, Applicants respectfully submit that claims 1 to 7 would not have been obvious in view of the Sandborn reference, alone or in combination with any of the Sandborn patent or Berkow.

Regarding claims 7 to 18

In regard to claim 7 and dependent claims 8 to 18, the Sandborn reference does not teach or suggest a method for reducing toxicity associated with 6-MP drug treatment of an immune-mediated gastrointestinal disorder by administering a 6-MP drug to a subject having an immune-mediated gastrointestinal disorder and determining a level of a 6-MP metabolite in the subject, where a level of 6-MP metabolite greater than a

predetermined toxic level indicates a need to decrease the amount of 6-MP drug subsequently administered to the subject, thereby reducing toxicity associated with 6-MP drug treatment of the immune-mediated gastrointestinal disorder. Absent such a teaching or suggestion, the Sandborn reference cannot render the claimed invention obvious.

In regard to the Sandborn patent, this reference, as discussed above, merely describes the levels of 6-thioguanine nucleotide and 6-methylmercaptopurine associated with a specific AZA treatment regimen. However, the Sandborn patent does not teach or suggest the claimed methods of reducing toxicity associated with 6-MP drug treatment by determining a level of a 6-MP metabolite, where a level greater than a predetermined toxic level indicates a need to decrease the amount of 6-MP drug subsequently administered.

In regard to the predetermined toxic level of 6-TG, as described above, the Sandborn patent actually teaches away from the claimed invention by describing a minimal level of 6-TG, 400 pmol/$8x10^8$ RBCs, that is the predetermined toxic level of 6-TG recited in claim 12. The Sandborn patent also teaches away from the claimed invention in regard to 6-MMP levels. Specifically, the Sandborn patent indicates that 6-methylmercaptopurine is preferably about 1000 to 7000 pmol/10^8 RBCs (column 2, lines 54-57), which equals 8000 to 56,000 pmol/$8x10^8$ RBCs. In contrast, the predetermined toxic level of 6-MMP recited in claim 15 is about 7000 pmol/$8x10^8$ RBCs. Thus, the preferred level of 6-MMP described in the Sandborn patent is higher than the predetermined

toxic level of 6-MMP recited in the claims. Thus, the Sandborn patent teaches away from the predetermined 6-TG toxic level of 400 pmol/8x10^8 RBCs recited in claim 12 and the predetermined 6-MMP toxic level of 7000 pmol/8x10^8 RBCs recited in claim 15 and cannot render the claimed methods obvious.

In regard to Berkow, this reference, as described above, merely states that treatment with azathioprine or 6-mercaptopurine may have side effects that should be monitored but fails to describe any relationship between 6-TG or 6-MMP levels and side effects. As such, Berkow does not teach or suggest the claimed method of reducing toxicity associated with 6-MP drug treatment by determining a level of a 6-MP metabolite, where a level greater than a predetermined toxic level indicates a need to decrease the amount of 6-MP drug subsequently administered.

Therefore, Applicants respectfully submit that claims 7 to 18 would not have been obvious in view of the Sandborn reference, alone or in combination with any of the Sandborn patent or Berkow.

Regarding claims 19 to 29

In regard to claim 19 and dependent claims 20 to 29, the Sandborn reference does not teach or suggest a method for optimizing therapeutic efficacy and reducing toxicity associated with 6-MP drug treatment of an immune-mediated gastrointestinal disorder by administering a 6-MP drug to a subject having an

immune-mediated gastrointestinal disorder, determining a level of 6-TG in the subject, and determining a level of 6-methyl-mercaptopurine (6-MMP) in the subject, where a level of 6-TG less than a predetermined minimal therapeutic level indicates a need to increase the amount of 6-MP drug subsequently administered to the subject, thereby increasing therapeutic efficacy, where a level of 6-TG greater than a predetermined toxic level indicates a need to decrease the amount of 6-MP drug subsequently administered to the subject, thereby reducing toxicity associated with 6-MP drug treatment, and where a level of 6-MMP greater than a predetermined toxic level of 6-MMP indicates a need to decrease the amount of 6-MP drug subsequently administered to the subject, thereby reducing toxicity associated with 6-MP drug treatment of the immune-mediated gastrointestinal disorder. Absent such a teaching or suggestion, the Sandborn reference cannot render the claimed methods obvious.

In regard to the Sandborn patent, this reference, as discussed above, merely describes the levels of 6-thioguanine nucleotide and 6-methylmercaptopurine associated with a specific AZA treatment regimen. However, the Sandborn patent does not teach or suggest the claimed methods of optimizing therapeutic efficacy and reducing toxicity associated with 6-MP drug treatment by determining a level of a 6-TG and 6-MMP, where a level less than a predetermined minimal therapeutic level of 6-TG indicates a need to increase the amount of 6-MP drug subsequently administered and where a level greater than a predetermined toxic level of 6-TG and 6-MMP indicates a need to decrease the amount of 6-MP drug subsequently administered.

In regard to the predetermined minimal therapeutic level specifically recited in claims 23 and 26, the Sandborn reference actually teaches away from the claimed invention in that the preferred level of 6-TG is significantly higher than the predetermined minimal therapeutic level of about 230 pmol/$8x10^8$ RBCs. In regard to the predetermined toxic level of 6-TG, the Sandborn patent also teaches away from the claimed invention by describing a minimal level of 6-TG, 400 pmol/$8x10^8$ RBCs, that is the predetermined toxic level of 6-TG recited in dependent claims 24 and 26. Moreover, the Sandborn patent further teaches away from the claimed invention in that the preferred level of 6-MMP described in the Sandborn patent is higher than the predetermined toxic level of 6-MMP recited in the claims 25 and 26. Thus, the Sandborn patent teaches away from the recited predetermined minimal therapeutic level of 6-TG of 230 pmol/$8x10^8$ RBCs, the recited predetermined toxic level of 6-TG of 400 pmol/$8x10^8$ RBCs, and the recited predetermined toxic level of 6-MMP of 7000 pmol/$8x10^8$ RBCs and cannot render the claimed methods obvious.

In regard to Berkow, this reference, as described above merely states that treatment with azathioprine or 6-mercaptopurine may have side effects that should be monitored but fails to describe any relationship between 6-TG or 6-MMP levels and side effects. As such, Berkow does not teach or suggest the claimed method of reducing toxicity associated with 6-MP drug treatment by determining a level of a 6-MP metabolite, where a level greater than a predetermined toxic level indicates

a need to decrease the amount of 6-MP drug subsequently administered.

Therefore, Applicants respectfully submit that claims 19 to 29 would not have been obvious in view of the Sandborn reference, alone or in combination with any of the Sandborn patent or Berkow.

Regarding claims 30 to 34

In regard to claim 30 and dependent claims 31 to 34, the Sandborn reference does not teach or suggest a method of optimizing therapeutic efficacy of 6-MP drug treatment of non-IBD autoimmune disease by administering a 6-MP drug to a subject and determining a level of 6-TG, where a level less than a minimal therapeutic level indicates a need to increase the amount of 6-MP drug subsequently administered and where a level greater than a predetermined toxic level indicates a need to increase the amount of 6-MP drug subsequently administered. Absent such a teaching or suggestion, the Sandborn reference cannot render the claimed methods obvious.

In regard to the Sandborn patent, this reference, as discussed above, merely describes the levels of 6-thioguanine nucleotide and 6-methylmercaptopurine associated with a specific AZA treatment regimen. However, the Sandborn patent does not teach or suggest the claimed methods of optimizing therapeutic efficacy of 6-MP drug treatment by determining a level of 6-TG, where a level less than a minimal therapeutic level of 6-TG

indicates a need to increase the amount of 6-MP drug subsequently administered and where a level greater than a predetermined toxic level of 6-TG indicates a need to decrease the amount of 6-MP drug subsequently administered. In regard to the predetermined minimal therapeutic level specifically recited in claim 31, the Sandborn reference actually teaches away from the claimed invention in that the preferred level of 6-TG is significantly higher than the predetermined minimal therapeutic level of about 230 pmol/$8x10^8$ RBCs. In regard to the predetermined toxic level of 6-TG, the Sandborn patent also teaches away from the claimed invention by describing a minimal level of 6-TG, 400 pmol/$8x10^8$ RBCs, that is the predetermined toxic level of 6-TG recited in dependent claim 32. Thus, the Sandborn patent teaches away from the recited predetermined 6-TG minimal therapeutic level of 230 pmol/$8x10^8$ RBCs and the recited predetermined 6-TG toxic level of 400 pmol/$8x10^8$ RBCs and cannot render the claimed methods obvious.

In regard to Berkow, this reference, as described above, merely states that treatment with azathioprine or 6-mercaptopurine may have side effects that should be monitored but fails to describe any relationship between 6-TG or 6-MMP levels and side effects. As such, Berkow does not teach or suggest the claimed method of reducing toxicity associated with 6-MP drug treatment by determining a level of a 6-MP metabolite, where a level greater than a predetermined toxic level indicates a need to decrease the amount of 6-MP drug subsequently administered.

Therefore, Applicants respectfully submit that claims 30 to 34 would not have been obvious in view of the Sandborn reference, alone or in combination with any of the Sandborn patent or Berkow.

In summary, Applicants respectfully submit that the cited references do not teach or suggest the claimed methods of optimizing therapeutic efficacy and/or reducing toxicity associated with 6-MP drug treatment of an immune-mediated gastrointestinal disorder or non-IBD autoimmune disease by determining a level of a 6-MP metabolite, where a level less than a predetermined minimal therapeutic level indicates a need to increase the amount of 6-MP drug subsequently administered and where a level greater than a predetermined toxic level indicates a need to decrease the amount of 6-MP drug subsequently administered. Therefore, Applicants respectfully submit that the claimed methods would not have been obvious to one of ordinary skill in the art at the time the invention was made in view of the Sandborn reference, alone or in combination with any of the Sandborn patent or Berkow. Accordingly, Applicants respectfully request that the Examiner remove this ground for rejecting the claims under 35 U.S.C. § 103(a).

CONCLUSION

In light of the remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent or Cathryn Campbell if there are any questions.

Respectfully submitted,

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